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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/096,500	06/12/98	ASHKENAZI	A P1110P1

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EXAMINER	
KAUFMAN,C	
ART UNIT	**PAPER NUMBER**
1646	14

DATE MAILED: 09/25/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

PTO-90C (Rev. 2/95)

1- File Copy

Office Action Summary	Application No.	Applicant(s)	
	09/096,500	ASHKENAZI ET AL.	
	Examiner	Art Unit	
	Claire M. Kaufman	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

1)☒ Responsive to communication(s) filed on *06 July 2000* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15-34 and 50-52* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *29-34* is/are allowed.

6)☒ Claim(s) *15-28 and 50-52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of the CERTIFIED copies of the priority documents have been:

1.☐ received.

2.☐ received in Application No. (Series Code / Serial Number) _____ .

3.☐ received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15)☒ Notice of References Cited (PTO-892)
16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 10 .
18)☐ Interview Summary (PTO-413) Paper No(s). _____ .
19)☐ Notice of Informal Patent Application (PTO-152)
20)☐ Other: .

DETAILED ACTION

The amendment filed 7/6/00 has been entered.

Response to Arguments

The rejection of claims 17-21 and 51 under 35 USC 112, second paragraph, for reciting "comprising an antibody" and "composition", respectively, is withdrawn in view of the amendment to the claims. Note that claim 51 remains rejected as set forth below.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Drawings

Applicants intention to correct drawings and amend the specification as necessary when formal drawings are submitted is acknowledged.

Claim Rejections - 35 USC § 112, Second Paragraph

Claims 15-24, 28 and 50-52 remain rejected under 35 U.S.C. 112, first paragraph, for the reasons of record set forth in the previous Office action (paper #9) beginning at the bottom of page 3.

Applicants argue that the specification provides a novel member (*i.e.*, APO-2 DcR) of the TNFR family and methods and techniques by which one can make or identify variants of that member, as well as description of how to make and identify antibodies against such variants, so no undue experimentation would be required to make the present invention. The argument has been fully considered, but is not persuasive. The claimed antibody can bind a antigenic site not present in the disclosed Apo-2 DcR of SEQ ID NO:1. Antibodies may bind as few as 6 amino acid-long stretches (*e.g.*, Lerner et al., Advances in Immunology, 1984, p. 15, first paragraph). Apo-2 DcR of SEQ ID NO:1 has 259 amino acids. A protein 95% identical could have 13 amino acids different and, therefore, could have a new antigenic site which has not been disclosed. Further, which regions of native Apo-2 DcR are and are not antigenic have not been disclosed so the skilled artisan could not predict which amino acids outside those regions could be altered while maintaining antigenicity of the native (*i.e.*, disclosed) molecule. It is not clear what if any

feature(s) of the disclosed Apo-2 DcR must be maintained by a variant with the exception of a certain structural relatedness. It is not clear how one would use an antibody that bound a variant but not the disclosed Apo-2 DcR if one did not know how to use the variant itself.

Applicants argue that anti-Apo-2 DcR blocking antibodies are also enabled because a detailed description of Apo-2 DcR, a ligand for the receptor, and a showing that ligand binding to Apo-2 DcR inhibits apoptotic ligand activity are taught in the specification, so screening for and obtaining antibodies which blocked Apo-2 DcR would not be undue. The argument has been fully considered, but is not persuasive. Applicants have provided an invitation to experiment without a reasonably expectation of success. No other blocking antibodies for highly related receptors were known. No blocking antibody to Apo-2 DcR had been produced. The requirements of the type of epitope to which an antibody must bind to Apo-2 DcR to block its activity were not know. Blocking of receptor activity, whether by an antibody or non-antibody protein, are complex because binding may or may not be in the ligand binding domain of the receptor and three dimensional structure of the receptor is typically involved in both epitope formation and in ligand binding. The instant specification has not provided information to allow the skilled artisan to make the claimed blocking antibody without undue experimentation, nor has guidance to make or examples of such an antibody been provided.

Claim Rejections - 35 USC § 112, Second Paragraph

Claims 15, 51 and dependent claims 16-28, 50 and 52 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 15 remains unclear because the metes and bounds of the claim cannot be determined because it is not clear what "binds" means.

Applicants argue that "the term is used in a general sense, and the person of ordinary skill in this art will readily understand that that term as used is not meant to be unduly limited so as to only refer to a single type of binding such as direct or indirect binding...." The argument has been fully considered, but is not persuasive. If the term is not mean to be so limiting, it remains unclear what meanings the term is meant to include. As a results, it is not clear what the metes and bounds of the claimed antibody are in view the vagueness of what it can bind.

Claim 51 remains indefinite for reciting the limitation "antibodies of claim 15" in line 3. There is insufficient antecedent basis for this limitation in the claim. Claim 15 is drawn to an antibody--singular not plural.

Applicants argue that amendment of claim 51 to recite "one or more of the ... antibodies of claim 15" overcomes this rejection. The argument has been fully considered, but is not persuasive. The claim still includes multiple antibodies of claim 15, but claim 15 is drawn only to a single antibody.

Claims 15, 22-24 and dependent claims 16-21, 25-28 and 50-52 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 15 is indefinite because the amendment makes it unclear what the extracellular domain (ECD) sequence is if it is not part of SEQ ID NO:1. The claim says that the ECD comprises amino acids 1 to x of an Apo-2DcR polypeptide, where x is any one of residues 161 to 236 of SEQ ID NO:1; however, that does not limit from what residue 1 is. It is unclear if residue 1 is also of SEQ ID NO:1 and the ECD sequence is a contiguous stretch of amino acids from 1 to x of SEQ ID NO:1 where x is any one of residue 161-236, or if it is a non-contiguous series of amino acids from SEQ ID NO:1, or if 1 to w is a contiguous amino acid stretch from a sequence other than SEQ ID NO:1 and that those amino acids are fused to x, etc.

Claims 22-24 as amended are indefinite because the metes and bounds are still unclear. It is unclear if "the same *in vitro* or *in vivo* activities" refers to <u>all</u> *in vitro* activities or *in vivo* activities or just some of the same activities. If it is intended that just some of the activities are necessary to meet the claim limitation, then the claim is indefinite because which activities and how many are necessary to meet the limitation is unclear.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 15-24 and 50-52 are rejected under 35 U.S.C. 102(b) as being anticipated by Hudziak et al. (WO 89/06692) in view of Applicants' admission that antibody binding may be indirect (p. 6, fourth paragraph of response filed 7/6/00) and that deposited monoclonal antibodies were obtained from hybridoma cells made from immunized mice (Example 13 of specification), and "human" or "humanized" antibodies can contain antibody regions from non-human species such as mouse (section 3, beginning p. 55 of specification).

Hudziak et al. teach a goat anti-mouse antibody (p. 32, line 11) which bound a monoclonal antibody produced by a mouse-derived hybridoma cell line (p. 31).

The goat anti-mouse antibody taught by Hudziak et al. (p. 32, line11) would reasonably be expected to bind an antibody that binds an Apo-2 DcR polypeptide in view of Applicants' admission that the claimed antibody does not need to directly bind Apo-2DcR. Since antibodies are commonly produced in mice (especially monoclonal antibodies from hybridoma cell lines) and since human antibodies can have mouse regions, a secondary anti-mouse antibody would bind any antibody made in mouse or containing regions of a mouse antibody. As the anti-mouse antibody is in solution, it is necessarily with a carrier.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Claire M. Kaufman, whose telephone number is (703) 305-5791. Dr. Kaufman can generally be reached Monday through Thursday from 8:30AM to 12:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached at (703) 308-6564.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294. NOTE: If applicant *does* submit a paper by fax, the original signed copy should be retained by the applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office. **Please** advise the examiner at the telephone number above before facsimile transmission.

cmk

September 21, 2000

LORRAINE SPECTOR
PRIMARY EXAMINER